REMARKS

Claims 1-26 were pending in the application. Claims 24-26 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1, 17, 18, 19, 20, 21, 22, and 23 have been amended, claims 15 and 16 have been canceled, and new claims 27-34 have been added. Accordingly, upon entry of this amendment, claims 1-14 and 17-34 will be pending.

Support for the amendment to the claims may be found throughout the specification, including the originally filed claims. In particular, support for new claim 27 may be found at page 17, lines 26-27 of Applicants' specification. Support for new claims 28-34 may be found in the specification at, for example, Figures 3 and 4.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Election/Restrictions

Applicants gratefully acknowledge the Examiner's withdrawal of the restriction of Claims 1-23 into inventive Groups I-VII. Applicants understand that claims 1-23 are presently being examined as they read on the species Ig epsilon and the species of the use of small molecules in screening. It is Applicants understanding that the search will be extended to the remaining species upon a finding of allowability.

Specification

The Examiner has objected to the specification because "Figure 8 is referred to with reference to IgE and IgG probes. Figure 8 is a depiction of a vector."

Applicants respectfully traverse the foregoing objection to the specification. The description of Figure 8 in Applicants' specification at page 4, line 1 reads: "Figure 8 depicts a commercially available vector for the production of the RPPs of the invention." Figure 8 is a depiction of a vector, as described in the Figure legend. Figure 8 is not referred to with reference to IgE and IgG probes. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection.

Rejection of Claims 1-23 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-23 under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "the term "substantially complementary" in claim 1 is a relative term that renders the claim indefinite. The term is not defined by the claims, and is not adequately described in the specification (p. 17, lines 23-24) in such a manner that the skilled artisan would be able to ascertain the metes and bounds of the claimed invention."

Applicants respectfully traverse the foregoing rejection and submit that the pending claims are clear and definite when read by one of ordinary skill in the relevant art in combination with the teachings of the specification. Applicants' specification, at page 17, lines 23-29, states that

> by "substantially complementary" herein is meant that the probes are sufficiently complementary to the target sequence to hybridize under normal reaction conditions. ***Preferably, this complementarity is high enough to provide specificity, such that one probe will not hybridize to more than one transcript.*** In a preferred embodiment, the RPA probe sequences and target transcripts have less than 5 base mismatches, more preferably less than 3 base mismatches, and most preferably the RPA probe and the target transcript comprise complementary sequences having no base mismatches. (Emphasis added).

Contrary to the Examiner's assertion, Applicants specification does not merely recite various hybridization parameters. Applicants' specification defines "substantially complementary" to mean that the probes must be sufficiently complementary to ***specifically hybridize*** to a certain transcript without hybridizing to additional transcripts, regardless of the hybridization conditions chosen. Applicants submit that one of ordinary skill in the art would be capable of determining appropriate hybridization conditions for use in an assay. Thus, the definition of "sufficiently complementary,"as set forth in Applicants' specification, distinctly defines the metes and bounds of the invention. Based on this definition, one of ordinary skill in the art would understand the scope of the invention to include the use of probes which specifically bind to a target transcript. Accordingly, based on the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejection of Claims 1-23 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-23 under 35 U.S.C. §112, first paragraph "as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "the term "substantially complementary" in claim 1 is a relative term that renders the claims indefinite. The term is not defined by the claims, and is not adequately described in the specification (p. 17, lines 23-24) in such a manner that the skilled artisan would be able to ascertain the metes and bounds of the claimed invention."

Applicants respectfully point out that the Examiner indicates that this rejection is a written description rejection, but the description of the rejection is based on indefiniteness, at least in part. Accordingly, Applicants assume that the portion of the instant rejection pertaining to 35 USC §112, second paragraph was made in error, and respectfully requests clarification by the Examiner. However, based on the remainder of the Examiner's statements, Applicants assume that the instant rejection is a written description rejection.

The Examiner further states that

> [t]here is no guidance as to what constitutes 'normal reaction conditions,' thus the 'definition' is open-ended. In fact the specification goes on to say that 'stringent conditions are sequence-dependent and will be different in different circumstances.' The patent specification does not describe the invention in sufficient detail that one skilled in the art could clearly conclude that 'the inventor invented the claimed invention,' and was in possession of the full scope of the claimed invention.

Applicants respectfully traverse the foregoing rejection.

In determining whether the Written Description requirement is met, the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" published in the Federal Register on January 5, 2001 state that the Examiner should:

> compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (citing to Wang Labs v. Toshiba Corp., (Fed. Cir. 1993) 993 F.2d 858, 865). . . . Information which is well known in the art need not be described in detail in the specification. (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380).

Page 1105.

At page 1106, the Guidelines further state that "[t]he description need only describe in detail that which is new or not conventional (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380). In addition, Applicants note that "[a] specification may, within the meaning of 35 U.S.C., § 112, First Paragraph, contain a written description of a broadly written claimed invention ***without describing all species that claim encompasses***." *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988).

Applicants respectfully submit that the specification contains a written description of the claimed invention that would reasonably convey to one of skill in the art that Applicants had possession of the claimed invention at the time the application was filed. As set forth above, Applicants' specification, at page 17, lines 23-29, states that

> by "substantially complementary" herein is meant that the probes are sufficiently complementary to the target sequence to hybridize under normal reaction conditions. ***Preferably, this complementarity is high enough to provide specificity, such that one probe will not hybridize to more than one transcript.*** In a preferred embodiment, the RPA probe sequences and target transcripts have less than 5 base mismatches, more preferably less than 3 base mismatches, and most preferably the RPA probe and the target transcript comprise complementary sequences having no base mismatches. (Emphasis added).

Applicants' specification defines "substantially complementary" to mean that the probes must be sufficiently complementary to ***specifically hybridize*** to a certain transcript without hybridizing to additional transcripts. Thus, one of ordinary skill in the art would recognize that this definition excludes probes which do not specifically hybridize to a target sequence. Also, Applicants' specification provides examples of probes and target sequences which would be substantially complementary, *e.g.*, the RPA probe sequences and target transcripts have less than 5 base mismatches, less than 3 base mismatches, or no base mismatches. Moreover, one of ordinary skill in the art would be able to identify which probes provide specificity and to determine optimal conditions for conducting the assay. Therefore, Applicants respectfully submit that the claimed invention is adequately described. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

The Examiner has also rejected claims 1-23 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" In particular, the Examiner is of the opinion that "[t]he specification disclosure does not sufficiently teach (*i.e.*, adequately describe) the method because it does not teach:

A. Quantification without the use of a labeled probe
B. Identification of a candidate agent
C. Identification of a candidate agent in combination with quantification without the use of a labeled probe."

Applicants respectfully traverse the foregoing rejection and submit that the specification contains a written description of the claimed invention that would reasonably convey to one of skill in the art that Applicants had possession of the claimed invention at the time the application was filed.

Claim 1 is directed to a method for determining whether a candidate agent is capable of modulating germline transcription, comprising adding a candidate agent to a plurality of cells; preparing mRNA from the plurality of cells to form an mRNA mixture; adding to the mixture at least a first RNAse protection probe (RPP) substantially complementary to a first germline mRNA from an immunoglobulin heavy chain gene locus to form a first hybridization complex between the first germline mRNA and the first RPP; adding an RNAse protection enzyme (RPE) to the mixture, such that mRNA that is not protected is digested; and quantifying the amount of said first germline mRNA as compared to a cell in the absence of a candidate agent to thereby identify a candidate agent that alters the amount of the first germline mRNA.

The Examiner states that Applicants' specification does not provide written description for "quantification without the use of a labeled probe." Applicants respectfully submit that Applicants' specification discloses methods for quantification of the germline transcript other than through the use of a labeled probe. For example, Applicants specification, at page 24, line 27 through page 25, line 3, states that

> [o]nce the non-hybridized mRNA (*i.e.*, single stranded) is digested away or removed, the amount of germline transcript (hybridized to RPA probe) is detected and/or quantified. ***This can be done in a***

> ***variety of ways, and can be done with denaturation into single stranded forms if required. Frequently gel electrophoresis is used, although other types of size exclusion techniques may be used, or other separations steps. The amount of germline transcript present is inferred by determining the amount of RPA probe protected from RNAse digestion. Quantification can be done by normalizing to the level of RNAse protected transcripts of housekeeping genes between samples*** (Emphasis added).

As set forth above, the amount of germline transcript can be quantified in a number of ways, including, for example, detecting the size of the germline transcript using size exclusion techniques or quantitative PCR techniques which were well known in the art at the time the application was filed. Although use of a labeled probe can facilitate such analyses, it is not required. Accordingly, based on the foregoing, Applicants specification provides adequate written description for quantification of germline RNA without the use of a labeled probe.

The Examiner is also of the opinion that Applicants' specification does not provide written description for "[i]dentification of a candidate agent." The Examiner asks "[h]ow is the library deconvoluted from the preferred embodiments of 10^6-10^9 candidate agents to at least one (or several, or several dozen, or several hundred) candidate agent(s)." This rejection is also respectfully traversed.

Applicants acknowledge that the testing of only one compound at a time simplifies identification of hits, however, it is well known in the art that the huge number of compounds produced by combinatorial chemistry makes the testing of "pooled" compounds inevitable. It has become standard industry practice to re-test members of an active pool to identify the compound in the pool that possesses the activity. Applicants contend that one of skill in the art at the time the application was filed would have understood the nature of screening assays and that point out that what is well known in the art need not be described in detail in the specification (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380). However, in an effort to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 1 such that it is directed to a method for determining whether ***a candidate agent*** is capable of modulating germline transcription, comprising adding a candidate agent to a plurality of cells, rather than adding a ***library of candidate agents***. Accordingly, Applicants respectfully submit that the claimed invention is adequately described with respect to the identification of a candidate agent.

With respect to "the identification of a candidate agent in combination with quantification without the use of a labeled probe," Applicants refer to the arguments made *supra* and respectfully submit that Applicants' specification adequately describes the identification of a candidate agent capable of modulating germline transcription.

The Examiner has further rejected claims 1-23 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was field, had possession of the claimed invention." In particular, the Examiner is of the opinion that the specification and the originally filed claims do not provide support for the amendment to claim 1 which reads "from an immunoglobulin heavy chain gene locus."

The subject matter of claim 1 is set forth above. Applicants respectfully traverse the foregoing rejection and submit that the phrase "first germline mRNA ***from an immunoglobulin heavy chain gene locus***" does not constitute new matter and is adequately described in Applicants' specification. Applicants point out that there are numerous examples of the detection of germline mRNA from an immunoglobulin heavy chain gene locus, e.g., from IgE, IgA1, IgA2, IgGg1, IgG2, IgG3, and IgG4 loci, in the specification. Identical description of the claimed invention in the specification is not required. "It is not necessary that the claimed subject matter be described identically, but the disclosure originally filed must convey to those skilled in the art that applicant had invented the subject matter later claimed..." (*In re Wilder*, 736 F. 2d 1516, 222 USPQ 369 (Fed. Cir. 1984). Applicants further point out that the term is further supported, *e.g.*, in the instant Example (see, e.g., page 26, lines 4-9), where the development of primers from the heavy chain constant region is described.

The Examiner has further rejected claims 1-23 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. In particular, the Examiner is of the opinion that "the limitations of (A) 'A library of candidate agents,' (B) 'A plurality of cells'" and (C) 'identifying at least one candidate agent that alters the amount of said first germline mRNA' are not sufficiently described in the specification so as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Applicants respectfully traverse the foregoing rejection. Claim 1 is directed to a method for determining whether a candidate agent is capable of modulating germline transcription, comprising

adding a candidate agent to a plurality of cells; preparing mRNA from the plurality of cells to form an mRNA mixture; adding to the mixture at least a first RNAse protection probe (RPP) substantially complementary to a first germline mRNA from an immunoglobulin heavy chain gene locus to form a first hybridization complex between the first germline mRNA and the first RPP; adding an RNAse protection enzyme (RPE) to the mixture, such that mRNA that is not protected is digested; and quantifying the amount of said first germline mRNA as compared to a cell in the absence of a candidate agent to thereby identify a candidate agent that alters the amount of the first germline mRNA.

The Examiner is of the opinion that Applicants' specification "does not provide any guidance in the way of selecting a particular "candidate agent" (*i.e.*, Applicants provide no examples of candidate compounds...)." Applicants' specification states that a candidate bioactive agent includes any molecules "*e.g.*, protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc. that can be screened for activity as outlined herein" (page 5, lines 27-29). The specification goes on to describe, in great detail, examples of candidate compounds as well as examples of libraries of candidate compounds which may be used in the claimed methods of the invention (see, for example, page 5, line 32 through page 9, line 31 of Applicants' specification).

With respect to the narrowing of the number of candidate compounds to a smaller list of candidates, Applicants refer to the comments made *supra* with respect to art recognized methods of pooling agents to reduce the number of screening assays that need to be performed to assay a library of candidate agents. In addition, Applicants point out that the claims as amended embrace the use of one compound, eliminating the need for pooling.

In contrast to the Genentech case cited by the Examiner, the instant specification provides much more than "a starting point, a direction for future research." To the contrary, Applicants' specification provides specific guidance regarding the methods of the invention. RNAse probe protection assays were known in the art at the time the application was filed. Furthermore, Applicants' specification describes the preparation and use of specific RNAse protection probes (RPPs) which may be used in the methods of the invention (see page 17, line 11 through page 24, line 2; the Example, as well as Figures 3, 4, 5, and 6) and examples of candidate agents for use in the claimed methods (see page 5, line 32 through page 9, line 31 of Applicants' specification).

With respect to the Wands factors, Applicants would like to make the following remarks of record:

Breadth of the Claims and the Nature of the Invention

The Examiner is of the opinion that "[t]he claims are drawn to several broad genera. Applicant's claims place no structural limitations on the "candidate agents" that can be used in the claimed method...Applicant's claims place no limitations on the "plurality of cells" that can be used in the claimed method."

None of the pending claims are directed to candidate agents or cells. Rather the claims are directed to ***methods***, in particular, methods for determining whether a candidate agent is capable of modulating germline transcription by quantifying the amount of germline mRNA in a cell contacted with a candidate agent as compared to a cell in the absence of a candidate agent.

According to claim 1, a candidate agent is added to a plurality of cells; RNAse protection probe (RPP) substantially complementary to a first germline mRNA from an immunoglobulin heavy chain gene locus is added to mRNA from the plurality of cells to form a hybridization complex between the germline mRNA and the RPP; an RNAse protection enzyme (RPE) is added to the mixture, and the amount of germline mRNA is quantified as compared to a cell in the absence of a candidate agent to identify a candidate agent that alters the amount of the first germline mRNA.

As set forth above, Applicants' specification states that a candidate bioactive agent includes any molecules "*e.g.,* protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc. that can be screened for activity as outlined herein" (page 5, lines 27-29). The specification also describes, in great detail, examples of candidate compounds as well as examples of libraries of candidate compounds which may be used in the claimed methods of the invention (see, for example, page 5, line 32 through page 9, line 31 of Applicants' specification).

With respect to the cells used in the methods of the invention, Applicants specification clearly describes examples of cells used in the methods of the invention at, for example, page 5, lines 4-16, including the number and types of cells used in the methods of the invention.

Accordingly, candidate agents and cells used in the methods of the invention are sufficiently described to enable one skilled in the art to make and use the invention commensurate in scope with the claims. Therefore, the claims are fully enabled across their breadth.

State of the Art and the Level of Predictability in the Art

The Examiner cites Qiu, *et al.* (1998) as evidence that "[a]ctivation of germline transcription is induced by relatively few, specific effectors. While ribonuclease protection assays have been known for some time, there are no examples of their use as a combinatorial screening tool. Therefore, the Examiner contends that the level of predictability in the art is low or absent."

As the Examiner has indicated, at the time the invention was made, RNAse protection assays were known in the art. The fact that germline transcription was known to be induced by few effectors does not render the instant invention unpredictable. As set forth above, the instant invention is a directed to a method for identifying further compounds which are capable of modulating germline transcription. With respect to the Examiner's indication that the claimed invention is directed to a use of ribonuclease protection assays as a combinatorial screen, Applicants' respectfully submit that the claims, as amended, are directed to the use of "a candidate agent," rather than a "library of candidate agents." Furthermore, based on Applicants' specification, one of ordinary skill in the art would be able to ascertain which candidate agents and cells may be used in the methods of the invention, as well as methods for quantifying germline mRNA in accordance with the methods of the invention. Thus, based on the teachings of the specification, in combination with the level of predictability in the art regarding RNAse protection assays at the time of the present invention, the experimentation required to perform the claimed assays would have been merely routine.

Amount of Direction Provided by the Inventor and the Existence of Working Examples

The Examiner is of the opinion that "Applicants have not provided a single working example demonstrating the use of an RNAse protection assay to identify an unknown (or known, for that matter!) effector of germline transcription....the single working "example" describes only the construction of DNA templates from which probes could be transcribed....[t]here are no examples of the use of the claimed invention with a single molecule, much less a library of molecules. There are, in fact, no examples of any kind" (Emphasis in original).

Applicants respectfully submit that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." (M.P.E.P. §2164.02; *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Applicants' specification provides detailed disclosure regarding the candidate agents and cells which may be used in the methods of the invention as well as a specific working example and specific sequences of RPPs which may be used in the methods of the

invention. In addition, methods for quantifying germline mRNA in accordance with the methods of the invention are described. Accordingly, Applicants' specification provides sufficient disclosure such that one or ordinary skill in the art would be able to practice the methods of the invention without undue experimentation.

Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

The Examiner is of the opinion that "[i]n this case, Applicants have not provided any working examples that would teach (i.e., adequately describe) this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed."

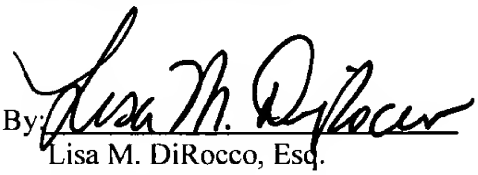
In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. As set forth above, Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed in the pending claims without undue experimentation. Accordingly, Applicants submit that the claimed invention is fully enabled by the disclosure in Applicants' specification and respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: 

Lisa M. DiRocco, Esq.
Registration No. 51,619
Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

Dated: December 24, 2003